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AMINO ACID DERIVATIVES

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(57) Claim

1. Amino acid derivatives of the formula I

$$X\text{-}Z\text{-}NR^2\text{-}CHR^3\text{-}CR^4\text{-}(CHR^5)_n\text{-}CO\text{-}E\text{-}NR^6\text{-}D \qquad I$$

wherein

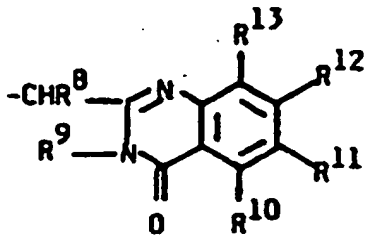
X is H, $R^1\text{-}O\text{-}C_mH_{2m}\text{-}CO\text{-}$, $R^1\text{-}C_mH_{2m}\text{-}O\text{-}CO\text{-}$, $R^1\text{-}C_mH_{2m}\text{-}CO\text{-}$, $R^1\text{-}SO_2\text{-}$ or $(R^1\text{-}C_mH_{2m}\text{-}(T)_x\text{-}C_rH_{2r})\text{-}L(R^7\text{-}C_pH_{2p})\text{-}C_tH_{2t}\text{-}CO\text{-}$,

Z is 0 to 4 amino acid radicals attached to one another by a peptide linkage and selected from the group consisting of Abu, Ada, Ala, BAla, Arg, Asn, Asp, Bia, Cal, Dab, Gln, Glu, Gly, His, N(im)-alkyl-His, Ile, Leu, tert.-Leu, Lys, Met, αNal, βNal, Nbg, Nle, Orn, Phe, Pro, Ser, Thr, Tic, Trp, Tyr and Val,

E is 0 to 2 amino acid radicals attached to one another by a peptide linkage and selected from the group consisting of Abu, Ala, Cal, His, Ile, Leu, Met, Nle, Phe, Trp, Tyr and Val,

D is $-CH_2\text{-}CHOH\text{-}CH_2OH$, $-C_zH_{2z}\text{-}SO_2\text{-}R^{14}$, a phenyl-

dyl-C_yH_{2y}- radical which is substituted by one or two R^{14}-SO_2- groups or an R^{14}-CO- group or an $(R^{14})_2$-PO- group and, if desired additionally by an Hal atom, or D is



R^1, R^3, R^7 and R^8 are each H, A, Ar, Ar-alkyl, Het, Het-alkyl or cycloalkyl having 3-7 C atoms, cycloalkylalkyl having 4-11 C atoms, bicycloalkyl or tricycloalkyl having in each case 7-14 C atoms or bicycloalkylalkyl or tricycloalkylalkyl having in each case 8-18 C atoms, each of which is unsubstituted or monosubstituted or polysubstituted by A, AO and/or Hal,

R^2, R^5 and R^6 are each H or A,

R^4 is (H, OH), (H, NH_2) or =O,

R^9 is H, NH_2, NHA or NA_2,

R^{10}, R^{11}, R^{12} and R^{13} are each H, Hal, OH, OA, NH_2, SH, SA, SO_2NH_2, CF_3, CN, COOH or COOA,

R^{14} is OH, OA, NH_2, NHA, NA_2, NHcycloalkyl having 3-7 C atoms, N(cycloalkyl)$_2$ having 6-14 C atoms, pyrrolidino, piperidino, hexahydroazepino, morpholino, thiomorpholino, piperazino, N-A-piperazino, NHAr or NHHet,

L is CH or N,

T is O, S, NH or NA,

n is 1 or 2,

m, p, r and t are each 0, 1, 2, 3, 4 or 5,

x is 0 or 1,

y is 0, 1 or 2,

z is 2, 3, 4, 5 or 6,

Ar is phenyl which is unsubstituted or mono-ubstituted

and/or NH_2 or unsubstituted naphthyl,

Het is a saturated or unsaturated 5-membered or 6-membered heterocyclic radical which has 1-4 N, O and/or S atoms, which can be condensed with a benzene ring and/or can be monosubstituted or polysubstituted by A, AO, Hal, CF_3, HO, O_2N, carbonyl oxygen, H_2N, HAN, A_2N, AcNH, AS, ASO, ASO_2, HOOC, AOOC, CN, H_2NCO, H_2NSO_2, ASO_2NH, Ar or Ar-alkenyl, hydroxyalkyl and/or aminoalkyl having in each case 1-8 C atoms, and/or in which the N and/or S heteroatoms can also be oxidized,

Hal is F, Cl, Br or I,

Ac is A-CO-, Ar-CO- or A-NH-CO-,

alkyl- is an alkylene group having 1-4 C atoms and

A is alkyl having 1-8 C atoms,

and wherein it is also possible for one or more -NA-CO- groups to replace one or more -NH-CO- groups, and salts thereof.

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COMPLETE SPECIFICATION

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Complete Specification for the invention entitled AMINO ACID DERIVATIVES.

The following statement is a full description of this invention including the best method of performing it known to me:-

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ASC 49

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6100 D a r m s t a d t

Amino acid derivatives

The invention relates to new amino acid derivatives of the formula I

$$X\text{-}Z\text{-}NR^2\text{-}CHR^3\text{-}CR^4\text{-}(CHR^5)_n\text{-}CO\text{-}E\text{-}NR^6\text{-}D \qquad I$$

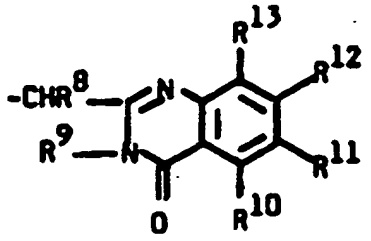
wherein

X is H, $R^1\text{-}O\text{-}C_mH_{2m}\text{-}CO\text{-}$, $R^1\text{-}C_mH_{2m}\text{-}O\text{-}CO\text{-}$, $R^1\text{-}C_mH_{2m}\text{-}CO\text{-}$, $R^1\text{-}SO_2\text{-}$ or $(R^1\text{-}C_mH_{2m}\text{-}(T)_x\text{-}C_rH_{2r})\text{-}L(R^7\text{-}C_pH_{2p})\text{-}C_tH_{2t}\text{-}CO\text{-}$,

Z is 0 to 4 amino acid radicals attached to one another by a peptide linkage and selected from the group consisting of Abu, Ada, Ala, βAla, Arg, Asn, Asp, Bia, Cal, Dab, Gln, Glu, Gly, His, N(im)-alkyl-His, Ile, Leu, tert.-Leu, Lys, Met, αNal, βNal, Nbg, Nle, Orn, Phe, Pro, Ser, Thr, Tic, Trp, Tyr and Val,

E is 0 to 2 amino acid radicals attached to one another by a peptide linkage and selected from the group consisting of Abu, Ala, Cal, His, Ile, Leu, Met, Nle, Phe, Trp, Tyr and Val,

D is $-CH_2\text{-}CHOH\text{-}CH_2OH$, $-C_zH_{2z}\text{-}SO_2\text{-}R^{14}$, a phenyl-$C_yH_{2y}$-, furyl-$C_yH_{2y}$-, thienyl-$C_yH_{2y}$- or pyridyl-$C_yH_{2y}$- radical which is substituted by one or two $R^{14}\text{-}SO_2$- groups or an $R^{14}\text{-}CO$- group or an $(R^{14})_2\text{-}PO$- group and, if appropriate, additionally by an Hal atom, or D is



R^1, R^3, R^7 and R^8 are each H, A, Ar, Ar-alkyl, Het, Het-alkyl or cycloalkyl having 3-7 C atoms, cycloalkylalkyl having 4-11 C atoms, bicycloalkyl or tricycloalkyl having in each case 7-14 C atoms or bicycloalkylalkyl or tricycloalkylalkyl having in each case 8-18 C atoms, each of which is unsubstituted or monosubstituted or polysubstituted by A, AO and/or Hal,

R^2, R^5 and R^6 are each H or A,

R^4 is (H, OH), (H, NH_2) or =O,

R^9 is H, NH_2, NHA or NA_2,

R^{10}, R^{11}, R^{12} and R^{13} are each H, Hal, OH, OA, NH_2, SH, SA, SO_2NH_2, CF_3, CN, COOH or COOA,

R^{14} is OH, OA, NH_2, NHA, NA_2, NHcycloalkyl having 3-7 C atoms, N(cycloalkyl)$_2$ having 6-14 C atoms, pyrrolidino, piperidino, hexahydroazepino, morpholino, thiomorpholino, piperazino, N-A-piperazino, NHAr or NHHet,

L is CH or N,

T is O, S, NH or NA,

n is 1 or 2,

m, p, r and t are each 0, 1, 2, 3, 4 or 5,

x is 0 or 1,

y is 0, 1 or 2,

z is 2, 3, 4, 5 or 6,

Ar is phenyl which is unsubstituted or monosubstituted or polysubstituted by A, AO, Hal, CF_3, OH, H_2NSO_2 and/or NH_2, or unsubstituted naphthyl,

Het is a saturated or unsaturated 5-membered or 6-membered heterocyclic radical which has 1-4 N, O and/or S atoms, which can be condensed with a benzene ring

and/or can be monosubstituted or polysubstituted by A, AO, Hal, CF_3, HO, O_2N, carbonyl oxygen, H_2N, HAN, A_2N, AcNH, AS, ASO, ASO_2, HOOC, AOOC, CN, H_2NCO, H_2NSO_2, ASO_2NH, Ar or Ar-alkenyl, hydroxyalkyl and/or aminoalkyl having in each case 1-8 C atoms, and/or in which the N and/or S heteroatoms can also be oxidized,

Hal is F, Cl, Br or I,

Ac is A-CO-, Ar-CO- or A-NH-CO-,

-alkyl- is an alkylene group having 1-4 C atoms and

A is alkyl having 1-8 C atoms,

and wherein it is also possible for one or more -NA-CO- groups to replace one or more -NH-CO- groups, and to salts thereof.

Similar compounds are known from EP-A-77,028.

The invention was based on the object of finding new compounds having valuable properties, especially compounds which can be used for the preparation of medicaments.

It has been found that the compounds of the formula I and their salts possess very valuable properties. Above all, they inhibit the activity of human plasma renin. This effect can be demonstrated, for example, by the method of F. Fyhrquist et al., Clin. Chem. 22, 250-256 (1976). It is remarkable that these compounds are very specific inhibitors of renin; as a rule substantially higher concentrations of these compounds are necessary for the inhibition of other aspartylproteinases (for example pepsin and cathepsin D).

The compounds can be employed as active compounds for medicaments in human and veterinary medicine, especially for the prophylaxis and treatment of cardiac, circulatory and vascular diseases, above all hypertension, cardiac insufficiency and hyperaldosteronism. In addition, the compounds can be used for diagnostic purposes in order to determine, in the case of patients with hypertension or hyperaldosteronism, the possible contribution made by the renin activity towards maintaining the pathological state.

The abbreviations of amino acid radicals listed above and below represent the radicals -NR'-R"-CO-, as a

rule -NH-CHR-CO-, (wherein R, R' and R" have the specific meaning known for each amino acid) of the following amino acids:

Abu	2-aminobutyric acid
Ada	3-adamantylalanine
Ala	alanine
βAla	β-alanine
Arg	arginine
Asn	asparagine
Asp	aspartic acid
Bia	3-(2-benzimidazolyl)-alanine
Cal	3-cyclohexylalanine
Dab	2,4-diaminobutyric acid
Gln	glutamine
Glu	glutamic acid
Gly	glycine
His	histidine
N(im)-alkyl-His	histidine which is substituted by A in the 1-position or 3-position of the imidazole ring
Ile	isoleucine
Leu	leucine
tert.-Leu	tert.-leucine
Lys	lysine
Met	methionine
αNal	α-naphthylalanine
βNal	β-naphthylalanine
Nbg	(2-norbornyl)-glycine
Nle	norleucine
N-Me-His	N-methylhistidine
N-Me-Phe	N-methylphenylalanine
Orn	ornithine
Phe	phenylalanine
Pro	proline
Ser	serine
Thr	threonine
Tic	tetrahydroisoquinoline-1-carboxylic acid
Trp	tryptophane
Tyr	tyrosine

Val valine.

The abbreviations below also have the following meanings:

BOC tert.-butoxycarbonyl

imi-BOM benzyloxymethyl in the 1-position of the imidazole ring

CBZ benzyloxycarbonyl

DNP 2,4-dinitrophenyl

imi-DNP 2,4-dinitrophenyl in the 1-position of the imidazole ring

ETNC N-ethylcarbamoyl

ETOC ethoxycarbonyl

FMOC 9-fluorenylmethoxycarbonyl

IPNC N-isopropylcarbamoyl

IPOC isopropoxycarbonyl

MC morpholinocarbonyl

OMe methyl ester

OEt ethyl ester

PBB 4-phenyl-2-benzylbutyryl

POA phenoxyacetyl

DCCI dicyclohexylcarbodiimide

HOBt 1-hydroxybenzotriazole.

Insofar as the amino acids mentioned above can exist in several enantiomeric forms, all these forms and also mixtures thereof (for example the DL-forms) are included in the above and following text, for example as a constituent of the compounds of the formula I. The L-forms are preferred. Where individual compounds are listed in the following text, the abbreviations of these amino acids relate in each case to the L-form, unless anything to the contrary is expressly indicated.

The invention also relates to a process for the preparation of an amino acid derivative of the formula I and salts thereof, characterized in that it is liberated from one of its functional derivatives by treatment with a solvolysing or hydrogenolysing agent, or in that a carboxylic acid of the formula II

$X\text{-}G^1\text{-}OH$

wherein G^1 is (a) Z^1,
(b) Z,
(c) Z-W,
(d) Z-W-E^1,
(e) Z-W-E and
W is $-NR^2-CHR^3-CR^4-(CHR^5)_n-CO-$
is reacted with an amino compound of the formula III
$H-G^2$ III
wherein G^2 is (a) $-Z^2-W-E-NR^6-D$,
(b) $-W-E-NR^6-D$,
(c) $-E-NR^6-D$,
(d) $-E^2-NR^6-D$,
(e) $-NR^6-D$,

E^1 and E^2 are each one amino acid radical selected from the group conisting of Abu, Ala, Cal, His, Ile, Leu, Met, Nle, Phe, Trp, Tyr and Val in such a manner that E^1 + E^2 together are E,

Z^1 and Z^2 are each 1 to 3 amino acid radicals selected from the group consisting of Abu, Ada, Ala, βAla, Arg, Asn, Asp, Bia, Cal, Dab, Gln, Glu, Gly, His N(im)-alkyl-His, Ile, Leu, tert -Leu, Lys, Met, αNal, βNal, Nbg, Nle, Orn, Phe, Pro, Ser, Thr, Tic, Trp, Tyr and Val in such a manner that Z^1 + Z^2 together are Z, and in that, if appropriate, a functionally modified amino and/or hydroxyl group in a compound of the formula I is liberated by treatment with solvolysing or hydrogenolysing agents and/or, in order to prepare a compound of the Formula I wherein R^4 = (H, OH) or (H, NH_2), an aminoketo acid derivative of the formula I wherein R^4 = O is reduced or reductively aminated and/or a radical D is converted into another radical D by treatment with esterifying, solvolysing or reducing agents and/or a compound of the formula I is converted into one of its salts by treatment with an acid.

In the preceding and following text, the radicals or parameters X, Z, E, D, R^1 to R^{14}, L, T, m, n, p, r, t, x, y, z, Ar, Het, Hal, Ac, A, G^1, G^2, E^1, E^2, Z^1, Z^2 and W have the meanings indicated in the formulae I, II or III, unless anything to the contrary is expressly indicated.

In the formulae above, A has 1 - 8, preferably 1, 2, 3 or 4, C atoms. A is preferably methyl and also ethyl, propyl, isopropyl, butyl, isobutyl, sec.-butyl or tert.-butyl, and also pentyl, 1-, 2- or 3-methylbutyl, 1,1-, 1,2- or 2,2-dimethylpropyl, 1-ethylpropyl, hexyl, 1-, 2-, 3- or

4-methylpentyl, 1,1-, 1,2-, 1,3-, 2,2-, 2,3- or 3,3-dimethylbutyl, 1-ethylbutyl, 2-ethylbutyl, 1-ethyl-1-methylpropyl, 1-ethyl-2-methylpropyl, 1,1,2-trimethylpropyl, 1,2,2-trimethylpropyl, heptyl or octyl.

Cycloalkyl is preferably cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl or cycloheptyl, but is also, for example, 1-, 2- or 3-methylcyclopentyl or 1-, 2-, 3- or 4-methylcyclohexyl.

Accordingly, cycloalkylalkyl is preferably cyclopropylmethyl, 2-cyclopropylethyl, cyclobutylmethyl, 2-cyclobutylethyl, cyclopentylmethyl, 2-cyclopentylethyl, cyclohexylmethyl or 2-cyclohexylethyl, but is also, for example, 1-, 2- or 3-methylcyclopentylmethyl or 1-, 2-, 3- or 4-methylcyclohexylmethyl.

Bicycloalkyl is preferably 1-decalyl, 2-decalyl, 2-bicyclo[2,2,1]heptyl or 6,6-dimethyl-2-bicyclo[3,1,1]heptyl.

Tricycloalkyl is preferably 1-adamantyl.

Hal is preferably F, Cl or Br, but also I.

Ac is preferably A-CO-, such as acetyl, propionyl or butyryl, Ar-CO-, such as benzoyl, o-, m- or p-methoxybenzoyl or 3,4-dimethoxybenzoyl, or A-NH-CO-, such as N-methylcarbamoyl or N-ethylcarbamoyl.

Ar is preferably phenyl and also preferably o-, m- or p-tolyl, o-, m- or p-ethylphenyl, o-, m- or p-methoxyphenyl, o-, m- or p-fluorophenyl, o-, m- or p-chlorophenyl, o-, m- or p-bromophenyl, o-, m- or p-iodophenyl, o-, m- or p-trifluoromethylphenyl, o-, m- or p-hydroxyphenyl, o-, m- or p-sulfamoylphenyl, 2,3-, 2,4-, 2,5-, 2,6-, 3,4- or 3,5-dimethoxyphenyl, 3,4,5-trimethoxyphenyl, o-, m- or p-aminophenyl, 1-naphthyl or 2-naphthyl.

Accordingly, Ar-alkyl is preferably benzyl, 1-phenylethyl, 2-phenylethyl, o-, m- or p-methylbenzyl, 1-o-, -m- or -p-tolylethyl, 2-o-, -m- or -p-tolylethyl, o-, m- or p-ethylbenzyl, 1-o-, -m- or -p-ethylphenylethyl, 2-o-, -m- or -p-ethylphenylethyl, o-, m- or p-methoxybenzyl, 1-o-, -m- or -p-methoxyphenylethyl, 2-o-, -m- or -p-methoxyphenylethyl, o-, m- or p-fluorobenzyl, 1-o-, -m- or p-fluoro-

phenylethyl, 2-o-, -m- or -p-fluorophenylethyl, o-, m- or p-chlorobenzyl, 1-o-, -m- or -p-chlorophenylethyl, 2-o-, -m- or -p-chlorophenylethyl, o-, m- or p-bromobenzyl, 1-o-, -m- or -p-bromophenylethyl, 2-o-, -m- or -p-bromophenylethyl, o-, m- or p-iodobenzyl, 1-o-, -m- or -p-iodophenylethyl, 2-o-, -m- or -p-iodophenylethyl, o-, m- or p-trifluoromethylbenzyl, o-, m- or p-hydroxybenzyl, 2,3-, 2,4-, 2,5-, 2,6-, 3,4- or 3,5-dimethoxybenzyl, 3,4,5-trimethoxybenzyl, o-, m- or p-aminobenzyl, 1-naphthylmethyl or 2-naphthylmethyl.

Het is preferably 2-furyl, 3-furyl, 2-thienyl, 3-thienyl, 1-, 2- or 3-pyrryl, 1-, 2-, 4- or 5-imidazolyl, 1-, 3-, 4- or 5-pyrazolyl, 2-, 4- or 5-oxazolyl, 3-, 4- or 5-isoxazolyl, 2-, 4- or 5-thiazolyl, 3-, 4- or 5-isothiazolyl, 2-, 3- or 4-pyridyl or 2-, 4-, 5- or 6-pyrimidyl, and is also preferably 1,2,3-triazol-1-yl, -4-yl or -5-yl, 1,2,4-triazol-1-yl, -3-yl or -5-yl, 1-tetrazolyl, 5-tetrazolyl, 1,2,3-oxadiazol-4-yl, 1,2,3-oxadiazol-5-yl, 1,2,4-oxadiazol-3-yl, 1,2,4-oxadiazol-5-yl, 1,3,4-thiadiazol-2-yl, 1,3,4-thiadiazol-5-yl, 1,2,4-thiadiazol-3-yl, 1,2,4-thiadiazol-5-yl, 2,1,5-thiadiazol-3-yl, 2,1,5-thiadiazol-4-yl, 2-, 3-, 4-, 5- or 6-2H-thiopyranyl, 2-, 3- or 4-4H-thiopyranyl, 3-pyridazinyl, 4-pyridazinyl, pyrazinyl, 2-, 3-, 4-, 5-, 6- or 7-benzofuryl, 2-, 3-, 4-, 5-, 6- or 7-benzothienyl, 1-, 2-, 3-, 4-, 5-, 6- or 7-indolyl, 1-, 2-, 3-, 4-, 5-, 6- or 7-isoindolyl, 1-, 2-, 4- or 5-benzimidazolyl, 1-, 3-, 4-, 5-, 6- or 7-benzopyrazolyl, 2-, 4-, 5-, 6- or 7-benzoxazolyl, 3-, 4-, 5-, 6- or 7-benzisoxazolyl, 2-, 4-, 5-, 6- or 7-benzthiazolyl, 2-, 4-, 5-, 6- or 7-benzisothiazolyl, 4-, 5-, 6- or 7-benz-2,1,3-oxadiazolyl, 2-, 3-, 4-, 5-, 6-, 7- or 8-quinolyl, 1-, 3-, 4-, 5-, 6-, 7- or 8-isoquinolyl, 1-, 2-, 3-, 4- or 9-carbazolyl, 1-, 2-, 3-, 4-, 5-, 6-, 7-, 8- or 9-acridinyl, 3-, 4-, 5-, 6-, 7- or 8-cinnolyl, 2-, 4-, 5-, 6-, 7- or 8-quinazolyl. The heterocyclic radicals can also be partly or completely hydrogenated. Het can, therefore, also be, for example: 2,3-dihydro-2-, -3-, -4- or -5-furyl, 2,5-dihydro-2-, -3-, -4- or 5-furyl, tetrahydro-2-furyl, tetrahydro-3-furyl, tetrahydro-2-thienyl, tetrahydro-

3-thienyl, 2,3-dihydro-1-, -2-, -3-, -4- or -5-pyrryl, 2,5-dihydro-1-, -2-, -3-, -4- or -5-pyrryl, 1-, 2- or 3-pyrrolidinyl, tetrahydro-1-, -2- or -4-imidazolyl, 2,3-dihydro-1-, -2-, -3-, -4- or -5-pyrazolyl, 2,5-dihydro-1-, -2-, -3-, -4- or 5-pyrazolyl, tetrahydro-1-, -3- or -4-pyrazolyl, 1,4-dihydro-1-, -2-, -3- or -4-pyridyl, 1,2,3,4-tetrahydro-1-, -2-, -3-, -4-, -5- or -6-pyridyl, 1,2,3,6-tetrahydro-1-, -2-, -3-, -4-, -5- or -6-pyridyl, 1-, 2-, 3- or 4-piperidinyl, 2-, 3- or 4-morpholinyl, tetrahydro-2-, -3- or -4-pyranyl, 1,4-dioxanyl, 1,3-dioxan-2-, -4- or -5-yl, hexahydro-1-, -3- or -4-pyridazinyl, hexahydro-1-, -2-, -4- or -5-pyrimidyl, 1-, 2- or 3-piperazinyl, 1,2,3,4-tetrahydro-1-, -2-, -3-, -4-, -5-, -6-, -7- or -8-quinolyl, 1,2,3,4-tetrahydro-1-, -2-, -3-, -4-, -5-, -6-, -7- or 8-isoquinolyl.

The heterocyclic radicals can also be substituted as indicated. Het can, therefore, preferably also be: 2-amino-4-thiazolyl, 4-carboxy-2-thiazolyl, 4-carbamoyl-2-thiazolyl, 4-(2-aminoethyl)-2-thiazolyl, 2-amino-5,6-dimethyl-3-pyrazinyl or 4-carbamoylpiperidino, and also, for example, 3-, 4- or 5-methyl-2-furyl, 2-, 4- or 5-methyl-3-furyl, 2,4-dimethyl-3-furyl, 5-nitro-2-furyl, 5-styryl-2-furyl, 3-, 4- or 5-methyl-2-thienyl, 2-, 4- or 5-methyl-3-thienyl, 3-methyl-5-tert.-butyl-2-thienyl, 5-chloro-2-thienyl, 5-phenyl-2- or -3-thienyl, 1-, 3-, 4- or 5-methyl-2-pyrryl, 1-methyl-4-nitro-2-pyrryl, 1-methyl-5-nitro-2-pyrryl, 3,5-dimethyl-4-ethyl-2-pyrryl, 4-methyl-5-pyrazolyl, 5-methyl-3-isoxazolyl, 3,4-dimethyl-5-isoxazolyl, 4-methyl-2-thiazolyl, 5-methyl-2-thiazolyl, 2-methyl-4-thiazolyl, 5-methyl-4-thiazolyl, 2-methyl-5-thiazolyl, 4-methyl-5-thiazolyl, 2,4-dimethyl-5-thiazolyl, 3-, 4-, 5- or 6-methyl-2-pyridyl, 2-, 4-, 5- or 6-methyl-3-pyridyl, 2- or 3-methyl-4-pyridyl, 3-, 4-, 5- or 6-chloro-2-pyridyl, 2-, 4-, 5- or 6-chloro-3-pyridyl, 2-chloro-4-pyridyl, 3-chloro-4-pyridyl, 2,6-dichloropyridyl, 2-hydroxy-3-, -4-, -5- or -6-pyridyl (= 1H-2-pyridon-3-, -4-, -5- or -6-yl), 5-phenyl-1H-2-pyridon-3-yl, 5-p-methoxyphenyl-1H-2-pyridon-3-yl, 2-methyl-3-hydroxy-4-hydroxymethyl-5-pyridyl, 2-hydroxy-4-amino-6-methyl-3-pyridyl, 3-N'-methylureido-1H-4-pyridon-5-yl, 4-

methyl-2-pyrimidyl, 4,6-dimethyl-2-pyrimidyl, 2-, 5- or 6-methyl-4-pyrimidyl, 2,6-dimethyl-4-pyrimidyl, 2,6-dihydroxy-4-pyrimidyl, 5-chloro-2-methyl-4-pyrimidyl, 2-methyl-4-amino-5-pyrimidyl, 3-methyl-2-benzofuryl, 2-ethyl-3-benzofuryl, 7-methyl-2-benzothienyl, 1-, 2-, 4-, 5-, 6- or 7-methyl-3-indolyl, 1-methyl-5- or -6-benzimidazolyl, 1-ethyl-5-benzimidazolyl, 1-ethyl-6-benzimidazolyl and 3-, 4-, 5-, 6-, 7- or 8-hydroxy-2-quinolyl.

R^1 and R^7 are preferably A, especially methyl, ethyl, propyl, isopropyl, butyl, isobutyl or tert.-butyl, and also, preferably, cyclopropyl, cyclopentyl, cyclohexyl, phenyl, benzyl, pyrrolidino, piperidino or morpholino.

R^2, R^5 and R^6 are preferably H or methyl, and also ethyl, propyl, isopropyl, butyl or isobutyl.

R^3 is preferably cyclohexylmethyl, and also preferably A, especially methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec.-butyl, pentyl, isopentyl (3-methylbutyl) or 2-methylbutyl, phenyl, benzyl, p-chlorobenzyl, 2-cyclohexylethyl, bicyclo[2,2,1]heptyl-2-methyl or 6,6-dimethylbicyclo[3,1,1]heptyl-2-methyl.

R^4 is preferably (H, OH).

R^8 is preferably isopropyl, isobutyl, sec.-butyl or benzyl, and also preferably H, methyl, ethyl, propyl, butyl or cyclohexylmethyl.

R^9 is preferably H or NH_2.

R^{10} and R^{13} are preferably H.

R^{11} is preferably H or SO_2NH_2.

R^{12} is preferably H or Cl.

R^{14} is preferably NH_2, $NHCH_3$ or $N(CH_3)_2$, and also preferably 2-thiazolylamino, 3-isoxazolylamino, 5-methyl-3-isoxazolylamino, 3,4-dimethyl-5-isoxazolylamino, 2-pyrimidylamino, 4-methyl-2-pyrimidylamino, 4,6-dimethyl-2-pyrimidylamino or 2,6-dimethyl-4-pyrimidylamino.

L is preferably CH.

T is preferably O or S.

The parameters m, p, r and t are preferably 0, 1 or 2; n is preferably 1; x is preferably 0; y is preferably 0 or 1; and z is preferably 2.

X is preferably H, POA, alkoxycarbonyl, such as ETOC, IPOC or BOC, CBZ, alkanoyl, such as acetyl, propionyl, butyryl or isobutyryl, cycloalkylcarbonyl, such as cyclopentylcarbonyl or cyclohexylcarbonyl, aroyl, such as benzoyl, arylalkanoyl, such as phenylacetyl, 2-phenylpropionyl, 3-phenylpropionyl, 4-phenylbutyryl, 2-benzyl-3-phenylpropionyl, PBB, 2-(2-phenylethyl)-4-phenylbutyryl, 2-(2-naphthylmethyl)-4-phenylbutyryl, 2-o-, -m- or -p-fluorophenylpropionyl, 3-o-, -m- or -p-fluorophenylpropionyl, 2-o-, -m- or -p-chlorophenylpropionyl, or 3-o-, -m- or -p-chlorophenylpropionyl, or cycloalkylalkanoyl, such as cyclohexylacetyl, 2-cyclohexylpropionyl or 3-cyclohexylpropionyl, or N-alkylcarbamoyl, such as ETNC or IPNC or MC. Radicals X which are particularly preferred are BOC and MC, and also ETOC, IPOC, ETNC, IPNC and PBB, and also H, POA, 4-phenylbutyryl, 2-benzyl-3-phenylpropionyl, 2-(2-phenylethyl)-4-phenylbutyryl, 2-(2-naphthylmethyl)-4-phenylbutyryl and CBZ. A further group of particularly preferred radicals X corresponds to the formula R^0-CH($CH_2C_6H_5$)-CO- wherein R^0 is pyrrolidino, piperidino, morpholino, alkyl, alkoxy or alkylthio each of which has 1-8 C atoms.

Z is preferably 2, but also 0 or 1 and also 3 or 4, amino acid radicals which are attached to one another by a peptide linkage, in particular one of the groups Gly, His, Phe-Gly, Phe-His, Pro-Phe-His or His-Pro-Phe-His, and also preferably one of the groups Abu, Ada, Asn, Bia, Cal, Gln, N-(im)-methyl-His, Leu, αNal, βNal, Nle, Phe, Trp, Tyr, Abu-His, Ada-His, Ala-His, Ala-Phe, Arg-His, Asn-His, Bia-His, Cal-His, Dab-His, Glu-His, Gly-His, His-His, Ile-His, Leu-His, tert.-Leu-His, Lys-His, Met-His, αNal-His, βNal-His, Nbg-His, Nle-His, (N-Me-His)-His, (N-Me-Phe)-His, Orn-His, Phe-Abu, Phe-Ada, Phe-Ala, Phe-Arg, Phe-Asn, Phe-Bia, Phe-Cal, Phe-Dab, Phe-Gln, Phe-Glu, Phe-(N-im-methyl-His), Phe-Ile, Phe-Leu, Phe-tert.Leu, Phe-Lys, Phe-Met, Phe-α-Nal, Phe-βNal, Phe-Nbg, Phe-Nle, Phe-(N-Me-His), Phe-(N-Me-Phe), Phe-Orn, Phe-Phe, Phe-Pro, Phe-Ser, Phe-Thr, Phe-Tic, Phe-Trp, Phe-Tyr, Phe-Val, Pro-His, Ser-His, Thr-His, Tic-His, Trp-His, Tyr-His, Val-His, and also Ada-Phe-His, Pro-Ala-

His, Pro-Ala-Phe, Pro-Phe-Ala, Pro-Phe-Phe, His-Pro-Ala-His, and also Pro-Abu-His, Pro-Ada-His, Pro-Arg-His, Pro-Asn-His, Pro-Bia-His, Pro-Dab-His, Pro-Glu-His, Pro-His-His, Pro-Ile-His, Pro-Leu-His, Pro-tert.-Leu-His, Pro-Lys-His, Pro-Met-His, Pro-Nbg-His, Pro-Nle-His, Pro-(N-Me-His)-His, Pro-(N-Me-Phe)-His, Pro-Orn-His, Pro-Phe-Abu, Pro-Phe-Ada, Pro-Phe-Arg, Pro-Phe-Asn, Pro-Phe-Bia, Pro-Phe-Dab, Pro-Phe-Gln, Pro-Phe-Glu, Pro-Phe-(N-im-methyl-His), Pro-Phe-Ile, Pro-Phe-Leu, Pro-Phe-tert.-Leu, Pro-Phe-Lys, Pro-Phe-Met, Pro-Phe-Nbg, Pro-Phe-Nle, Pro-Phe-(N-Me-His), Pro-Phe-(N-Me-Phe), Pro-Phe-Orn, Pro-Phe-Pro, Pro-Phe-Ser, Pro-Phe-Thr, Pro-Phe-Tic, Pro-Phe-Trp, Pro-Phe-Tyr, Pro-Phe-Val, Pro-Pro-His, Pro-Ser-His, Pro-Thr-His, Pro-Tic-His, Pro-Trp-His, Pro-Tyr-His, Pro-Val-His, His-Pro-Abu-His, His-Pro-Ada-His, His-Pro-Arg-His, His-Pro-Asn-His, His-Pro-Bia-His, His-Pro-Dab-His, His-Pro-Glu-His, His-Pro-His-His, His-Pro-Ile-His, His-Pro-Leu-His, His-Pro-tert.-Leu-His, His-Pro-Lys-His, His-Pro-Met-His, His-Pro-Nbg-His, His-Pro-Nle-His, His-Pro-(N-Me-His)-His, His-Pro-(N-Me-Phe)-His, His-Pro-Orn-His, His-Pro-Phe-Abu, His-Pro-Phe-Ada, His-Pro-Phe-Arg, His-Pro-Phe-Asn, His-Pro-Phe-Bia, His-Pro-Phe-Dab, His-Pro-Phe-Gln, His-Pro-Phe-Glu, His-Pro-Phe(N-im-methyl-His), His-Pro-Phe-Ile, His-Pro-Phe-Leu, His-Pro-Phe-tert.-Leu, His-Pro-Phe-Lys, His-Pro-Phe-Met, His-Pro-Phe-Nbg, His-Pro-Phe-Nle, His-Pro-Phe-(N-Me-His), His-Pro-Phe-(N-Me-Phe), His-Pro-Phe-Orn, His-Pro-Phe-Pro, His-Pro-Phe-Ser, His-Pro-Phe-Thr, His-Pro-Phe-Tic, His-Pro-Phe-Trp, His-Pro-Phe-Tyr, His-Pro-Phe-Val, His-Pro-Pro-His, His-Pro-Ser-His, His-Pro-Thr-His, His-Pro-Tic-His, His-Pro-Trp-His, His-Pro-Tyr-His, His-Pro-Val-His.

If X is one of the groups R^0-CH($CH_2C_6H_5$)-CO-, Z is preferably Gly or His.

E is preferably absent or is preferably Ile or Leu, and also preferably Abu, Cal, Met or Nle.

D is preferably $-CH_2-CHOH-CH_2OH$, $-(CH_2)_2SO_2NH_2$, -o-, -m- or especially $-p-C_6H_4-SO_2NH_2$, -o-, -m- or especially $-p-CH_2C_6H_4-SO_2NH_2$, -o-, -m- or especially $-p-C_6H_4-SO_2NHCH_3$, -o-, -m- or especially $-p-C_6H_4-SO_2N(CH_3)_2$, -o-, -m- or especially

-p-$C_6H_4SO_2NHHet$, -o-, -m- or especially p-$C_6H_4CONH_2$, 5-sulfamoyl-2-pyridyl, 2-sulfamoyl-5-thienyl or 3-sulfamoyl-5-thienyl, 3H-quinazolin-4-on-2-yl-CHR^8, 3-amino-3H-quinazolin-4-on-2-yl-CHR^8, 6-aminosulfonyl-7-chloro-3H-quinazolin-4-on-2-yl-CHR^8 or 3-amino-6-aminosulfonyl-7-chloro-3H-quinazolin-4-on-2-yl-CHR^8.

The group W is preferably -NH-CHR^3-CHOH-CH_2-CO-, especially -NH-CH(cyclohexylmethyl)-CHOH-CH_2-CO- ("AHCP", derived from 4-amino-3-hydroxy-5-cyclohexylpentanoic acid) and also -NH-CH(CH_2CH_2-cyclohexyl)-CHOH-CH_2-CO- ("AHCH"; derived from 4-amino-3-hydroxy-6-cyclohexylhexanoic acid), -NH-CH(isobutyl)-CHOH-CH_2-CO- ("Sta"; derived from statin) or -NH-CH(benzyl)-CHOH-CH_2-CO- ("AHPP"; derived from 4-amino-3-hydroxy-5-phenylpentanoic acid). The group W is also preferably -NH-CHR^3-CH(NH_2)-CH_2-CO-, especially -NH-CH(cyclohexylmethyl)-CH(NH_2)-CH_2-CO- ("DACP"; derived from 3,4-diamino-5-cyclohexylpentanoic acid), -NH-CH-(CH_2CH_2-cyclohexyl)-CH(NH_2)-CH_2-CO- ("DACH"; derived from 3,4-diamino-6-cyclohexylhexanoic acid), -NH-CH-(isobutyl)-CH(NH_2)-CH_2-CO- ("DAMH"; derived from 3,4-diamino-6-methylheptanoic acid) or -NH-CH(benzyl)-CH(NH_2)-CH_2-CO- ("DAPP"; derived from 3,4-diamino-5-phenylpentanoic acid).

The group W has at least one chiral centre. Further chiral centres can be present in the groups X, R^6 and D. The compounds of the formula I can, therefore, exist in various forms - optically inactive or optically active. The formula I embraces all these forms. If W is -NH-CHR^3-CR^4-CH_2-CO- in which R^4 is (H, OH) or (H, NH_2), the 3S-hydroxy-4S-amino enantiomers or 3S,4S-diamino enantiomers are preferred. Unless anything to the contrary is indicated in the designation of individual substances, the abbreviations AHCP, AHCH, Sta, AHPP, DACP, DACH, DAMH and DAPP relate in each case to the 3S,4S-forms.

Accordingly, the invention relates particularly to compounds of the formula I in which at least one of the radicals mentioned has one of the preferred meanings indicated above. Some preferred groups of compounds can be

expressed by means of the partial formulae Ia to Il following, which correspond to the formula I, but in which

in Ia X is H, BOC or R^0-CH($CH_2C_6H_5$)-CO-;

in Ib X is BOC;

in Ic Z is Gly, His, Phe-Gly or Phe-His;

in Id Z is Phe-Gly or Phe-His;

in Ie Z is Phe-His;

in If -NR^2-CHR^3-CR^4-$(CHR^5)_n$-CO- (= W) is AHCP;

in Ig E is absent;

in Ih R^6 is H;

in Ii X is H, BOC or R^0-CH($CH_2C_6H_5$)-CO-,
Z is Gly, His, Phe-Gly or Phe-His,
W is AHCP,
R^6 is H and
E is absent;

in Ij X is BOC,
Z is Phe-His or Phe-Gly,
W is AHCP,
R^6 is H and
E is absent;

in Ik X is BOC and
Z is Phe-Gly or Phe-His; and

in Il X is R^0-CH($CH_2C_6H_5$)-CO- and
Z is Gly or His.

Compounds of the following partial formulae are particularly preferred:

I* and Ia* to Il*, which correspond to the formulae I and Ia to Il, but in which

D is -CH_2-CHOH-CH_2OH, -p-C_6H_4-SO_2NH_2 or 3-R^9-5-R^{10}-6-R^{11}-7-R^{12}-8-R^{13}-3H-quinazolin-4-on-2-yl-CHR^8-;

I' and Ia' to Il', which correspond to the formulae I and Ia to Il, but in which

D is -CH_2-CHOH-CH_2OH;

I" and Ia" to Il", which correspond to the formulae I and Ia to Il, but in which

D is -p-C_6H_4-SO_2NH_2;

I'" and Ia'" to Il'", which correspond to the formulae I and Ia to Il, but in which

on-2-yl-CHR^8-,

R^8 is H, alkyl having 1-4 C atoms or benzyl,

R^9 is H or NH_2,

R^{10} and R^{13} are H,

R^{11} is H or SO_2NH_2 and

R^{12} is H or Cl;

I^0 and Ia^0 to Il^0, which correspond to the formulae I and Ia to Il, but in which

D is 3H-quinazolin-4-on-2-yl-CHR^8- or 3-amino-3H-quinazolin-4-on-2-yl-CHR^8- and

R^8 is H, alkyl having 1-4 C atoms or benzyl; and

I^{00} and Ia^{00} to Il^{00}, which correspond to the formulae I and Ia to Il, but in which

D is 3H-quinazolin-4-on-1-yl-CHR^8- or 3-amino-3H-quinazolin-4-on-2-yl-CHR^8- and

R^8 is sec.-butyl or isobutyl.

The compounds of the formula I and also the starting materials for their preparation are, incidentally, prepared by methods known per se, such as are described in the literature (for example in the standard works, such as Houben-Weyl, Methoden der organischen Chemie ("Methods of Organic Chemistry"), Georg-Thieme-Verlag, Stuttgart; and also EP-A-45,665, EP-A-77,028, EP-A-77,029 and EP-A-81,783), in particular under reaction conditions which are known and suitable for the reactions mentioned. In this regard it is also possible to make use of variants which are known per se, but are not mentioned here in detail.

If desired, the starting materials can also be formed in situ, so that they are not isolated from the reaction mixture, but are immediately reacted further to give the compounds of the formula I.

The compounds of the formula I are preferably obtained by liberating them from their functional derivatives by solvolysis, in particular hydrolysis, or by hydrogenolysis.

Preferred starting materials for the solvolysis or hydrogenolysis are those which otherwise correspond to the formula I, but, instead of one o- more free amino and/or

hydroxyl groups, contain corresponding protected amino and/or hydroxyl groups, preferably groups of this type which, instead of an H atom attached to an N atom, carry an amino protective group, for example those which correspond to the formula I, but, instead of an His group, contain an N-(im)-R^{15}-His group (wherein R^{15} is an amino protective group, for example BOM or DNP), or those of the formula X-Z-NR^2-CHR^3-$CH(NHR^{15})$-$(CHR^5)_n$-CO-E-NR^6-D.

Preferred starting materials are also those which, instead of the H atom of a hydroxyl group, carry a hydroxyl protective group, for example those of the formula X-Z-NR^2-CHR^3-$CHOR^{16}$-$(CHR^5)_n$-CO-E-NR^6-D, wherein R^{16} is a hydroxyl protective group.

It is also possible for several - identical or different - protected amino and/or hydroxyl groups to be present in the molecule of the starting material. If the protective groups present are different from one another, they can in many cases be split off selectively.

The term "amino protective group" is generally known and relates to groups which are suitable for protecting (blocking) an amino group against chemical reactions, but which can be removed readily after the desired chemical reaction has been carried out at another point on the molecule. Typical representatives of groups of this kind are, in particular, unsubstituted or substituted acyl, aryl (for example DNP), aralkoxymethyl (for example BOM) or aralkyl (for example benzyl, 4-nitrobenzyl or triphenylmethyl) groups. Since the amino protective groups are removed after the desired reaction (or reaction sequence), their nature and size is, incidentally, not critical; groups having 1-20, in particular 1-8, C atoms are, however, preferred. In the context of the present process, the term "acyl group", is to be understood in the widest sense. It embraces acyl groups derived from aliphatic, araliphatic, aromatic or heterocyclic carboxylic acids or sulfonic acids and also, in particular, alkoxycarbonyl, aryloxycarbonyl and, above all, aralkoxycarbonyl groups. Examples of acyl groups of this type are alkanoyl, such as acetyl, propionyl or buty-

ryl; aralkanoyl, such as phenylacetyl; aroyl, such as benzoyl or toluyl; aryloxyalkanoyl, such as POA; alkoxycarbonyl, such as methoxycarbonyl, ETOC, 2,2,2-trichloroethoxycarbonyl, BOC or 2-iodoethoxycarbonyl; and aralkyloxycarbonyl, such as CBZ ("carbobenzoxy"), 4-methoxybenzyloxycarbonyl or FMOC. Preferred amino protective groups are DNP and BOM, and also CBZ, FMOC, benzyl and acetyl.

The term "hydroxyl protective group" is also generally known and relates to groups which are suitable for protecting a hydroxyl group against chemical reactions, but which can be removed readily after the desired chemical reaction has been carried out at another point in the molecule. Typical representatives of such groups are the unsubstituted or substituted aryl, aralkyl or acyl groups mentioned above, and also alkyl groups. The nature and size of the hydroxyl protective groups is not critical, since they are removed again after the desired chemical reaction or reaction sequence; groups having 1-20, in particular 1-10, C atoms are preferred. Examples of hydroxyl protective groups are, inter alia: benzyl, p-nitrobenzoyl, p-toluenesulfonyl and acetyl, benzyl and acetyl being particularly preferred.

The functional derivatives of the compounds of the formula I to be used as starting materials can be prepared by customary methods of amino acid and peptide synthesis, such as are described, for example, in the standard works and patent applications mentioned, and also, for example, by the Merrifield solid phase method.

The liberation of the compounds of the formula I from their functional derivatives is effected - depending on the protective group used - with, for example, strong acids, preferably trifluoroacetic acid or perchloric acid, but also other strong inorganic acids, such as hydrochloric acid or sulfuric acid, strong organic carboxylic acids, such as trichloroacetic acid, or sulfonic acids, such as benzenesulfonic or p-toluenesulfonic acid. The presence of an additional inert solvent is possible, but not always necessary. Suitable inert solvents are preferably organic

solvents, for example carboxylic acids, such as acetic acid, ethers, such as tetrahydrofuran or dioxane, amides, such as dimethylformamide (DMF), halogenated hydrocarbons, such as methylene chloride, and also alcohols, such as methanol, ethanol or isopropanol, and also water. Mixtures of the abovementioned solvents are also suitable. Trifluoroacetic acid is preferably used in excess without the addition of a further solvent; perchloric acid is used in the form of a mixture of acetic acid and 70% perchloric acid in a 9 : 1 ratio. The reaction temperatures for the cleavage are preferably between about 0 and about 50°; the reaction is preferably carried out between 15 and 30° (room temperature).

The BOC group can be split off, for example, preferably by means of 40% trifluoroacetic acid in methylene chloride or by means of about 3 N to 5 N HCl in dioxane at 15-30°, while the FMOC group can be split off by means of an approximately 5 to 20% solution of dimethylamine, diethylamine or piperidine in DMF at 15-30°. Splitting off the DNP group is possible, for example, also by means of an approximately 3 to 10% solution of 2-mercaptoethanol in DMF/water at 15-30°.

Protective groups which can be removed by hydrogenolysis (for example BOM, CBZ or benzyl) can be split off, for example, by treatment with hydrogen in the presence of a catalyst (for example a noble metal catalyst such as palladium, preferably on a support such as charcoal). Suitable solvents for this reaction are those indicated above, in particular, for example, alcohols, such as methanol or ethanol, or amides, such as DMF. As a rule, the hydrogenolysis is carried out at temperatures between about 0 and 100° and pressures between about 1 and 200 bar, preferably at 20-30° and 1-10 bar. Hydrogenolysis of the CBZ group can be effected readily, for example, over 5 to 10% Pd/C in methanol at 20-30°.

Compounds of the formula I can also be obtained by direct peptide synthesis from a carboxylic acid component (formula II) and an amine component (formula III). Examples

of suitable carboxylic acid components are those of the partial formulae X-Z-OH, X-Z-W-OH or X-Z-W-E-OH, while suitable amine components are those of the partial formulae H-W-E-NR^6-D, H-E-NR^6-D or H-NR^6-D. The peptide bond can, however, also be made within the group Z or E; in this case a carboxylic acid of the formulae X-Z^1-OH or H-Z-W-E^1-OH with an amino compound of the formula H-Z^2-W-E-NR^6-D or H-E^2-NR^6-D, respectively, Z^1 + Z^2 being Z or E^1 + E^2 being E, respectively. This reaction is preferably carried out by customary methods of peptide synthesis, such as are described, for example, in Houben-Weyl, loc. cit., volume 15/II, pages 1 to 806 (1974).

The reaction is preferably carried out in the presence of a dehydrating agent, for example a carbodiimide, such as DCCI or dimethylaminopropylethylcarbodiimide, and also propanephosphonic anhydride (compare Angew. Chem. 92, 129 (1980)), diphenylphosphoryl azide or 2-ethoxy-N-ethoxycarbonyl-1,2-dihydroquinoline, in an inert solvent, for example a halogenated hydrocarbon, such as methylene chloride, an ether, such as tetrahydrofuran or dioxane, an amide, such as DMF or dimethylacetamide, or a nitrile, such as acetonitrile, at temperatures between about -10 and 40°, preferably between 0 and 30°.

Instead of II or III, it is also possible to employ in the reaction suitable reactive derivatives of these compounds, for example compounds in which reactive groups are blocked in the meantime by protective groups. The amino acid derivatives III can, for example, be used in the form of their activated esters, which are preferably formed in situ, for example by the addition of HOBt or N-hydroxysuccinimide.

The starting materials of the formulae II and III are for the most part known. Insofar as they are not known, they can be prepared by known methods, for example the above-mentioned methods of peptide synthesis and of splitting protective groups.

If desired, a functionally modified amino and/or hydroxyl group in a compound of the formula I can be liberated

by solvolysis or hydrogenolysis in accordance with one of the methods described above.

Thus it is possible, in particular, to convert a compound of the formula I wherein X is other than H into a compound of the formula I (X = H), preferably by hydrogenolysis, if X is CBZ, otherwise by selective solvolysis. If X is BOC, the BOC group can be split off, for example by means of HCl in dioxane at room temperature.

Furthermore, it is possible, for example, to reduce keto compounds of the formula I (R^4 = O) to compounds of the formula I (R^4 = H, OH)), for example by means of a complex metal hydride, such as $NaBH_4$, which does not simultaneously reduce the peptide carbonyl groups, in an inert solvent such as methanol at temperatures between about -10 and +30°.

Keto compounds of the formula I (R^4 = O) can also be converted into compounds of the formula I (R^4 = H, NH_2) by reductive amination. Reductive amination can be carried out in a single stage or in several stages. Thus it is possible, for example, to treat the keto compound with ammonium salts, for example ammonium acetate, and $NaCNBH_3$, preferably in an inert solvent, for example an alcohol such as methanol, at temperatures between about 0 and 50°, in particular between 15 and 30°. It is also possible first to convert the keto compound into the oxime in a customary manner by means of hydroxylamine, and to reduce this oxime to the amine, for example by catalytic hydrogenation over Raney nickel.

It is also possible to convert a radical D into another radical D by treatment with esterifying, solvolysing or reducing agents. Thus an acid can be esterified, for example by means of an alcohol of the formula A-OH or a diazoalkane, for example diazomethane, or an ester can be saponified to give the corresponding acid, for example by means of sodium hydroxide in aqueous dioxane solution at room temperature. It is also possible, for example, to convert a radical R^9 = NH_2 into a radical R^9 = H by treatment with reducing agents, preferably with Raney nickel in an

alcohol such as isopropanol at temperatures between 20 and 120°.

A base of the formula I can be converted into the appropriate acid addition salt by means of an acid. Acids suitable for this reaction are, in particular, those which afford physiologically acceptable salts. Thus it is possible to use inorganic acids, for example sulfuric acid, nitric acid, hydrogen halide acids, such as hydrochloric or hydrobromic acid, phosphoric acids, such as orthophosphoric acid, or sulfamic acid, and also organic acids, in particular aliphatic, alicyclic, araliphatic, aromatic or heterocyclic monobasic or polybasic carboxylic, sulfonic or sulfuric acids, for example formic acid, acetic acid, propionic acid, pivalic acid, diethylacetic acid, malonic acid, succinic acid, pimelic acid, fumaric acid, maleic acid, lactic acid, tartaric acid, malic acid, benzoic acid, salicylic acid, 2-phenylpropionic acid, 3-phenylpropionic acid, citric acid, gluconic acid, ascorbic acid, nicotinic acid, isonicotinic acid, methanesulfonic acid, ethanesulfonic acid, ethanedisulfonic acid, 2-hydroxyethanesulfonic acid, benzenesulfonic acid, p-toluenesulfonic acid, naphthalenemonosulfonic and naphthalenedisulfonic acids or laurylsulfuric acid. Salts with physiologically unacceptable acids, for example picrates, can be used to isolate and/or purify the compounds of the formula I.

The new compounds of the formula I and their physiologically acceptable salts can be used for the preparation of pharmaceutical formulations by bringing them into a suitable dosage form together with at least one excipient or auxiliary and, if desired, together with one or more further active compound(s). The formulations thus obtained can be employed as medicaments in human or veterinary medicine. Suitable excipients are organic or inorganic substances which are suitable for enteral (for example oral or rectal) administration or parenteral administration or for administration in the form of an inhalation spray, and which do not react with the new compounds, for example water, vegetable oils, benzyl alcohols, polyethylene gly-

cols, glycerol triacetate and other fatty acid glycerides, gelatine, soya lecithin, carbohydrates, such as lactose or starch, magnesium stearate, talc or cellulose. Tablets, coated tablets, capsules, syrups, elixirs or drops are especially used for oral administration; lacquered tablets and capsules having coatings or capsule casings resistant to gastric juices are of particular interest. Suppositories are used for rectal administration; solutions, preferably oily or aqueous solutions, and also suspensions, emulsions or implants are used for parenteral application. Sprays containing the active compound either dissolved or suspended in a propellent gas mixture (for example fluorochlorohydrocarbons) can be used for administration as an inhalation spray. It is preferable in this regard to use the active compound in a micronized form, and one or more additional physiologically tolerable solvents can be present, for example ethanol. Inhalation solutions can be administered by means of customary inhalers. The new compounds can also be lyophilized and the resulting lyophilisates can be used, for example, for the preparation of injection formulations. The formulations indicated can be sterilized and/or can contain auxiliaries, such as preservatives, stabilizers and/or wetting agents, emulsifiers, salts for influencing the osmotic pressure, buffer substances, colorants and/or aroma substances. If desired, they can also contain one or more further active compounds, for example one or more vitamins.

As a rule, the substances according to the invention are administered analogously to other known, commercially available peptides, but, in particular, analogously to the compounds described in EP-A-77,028, preferably in dosages between about 100 mg and 30 g, especially between 500 mg and 5 g, per dosage unit. The daily dosage is preferably between about 2 and 600 mg/kg of body weight. The particular dose for each specific patient depends, however, on a very wide variety of factors, for example on the effectiveness of the particular compound employed, on the age, body weight, general state of health, sex, diet, time and means

of administration, excretion rate, combination of medicaments and the severity of the particular disease to which the therapy applies. Parenteral administration is preferred.

In the preceding and following text all temperatures are quoted in °C. In the following examples "customary working up" means as follows: if necessary, water is added, the mixture is neutralized and extracted with ether or methylene chloride, the phases are separated, the organic phase is dried over sodium sulfate, filtered and evaporated, and the residue is purified by chromatography over silica gel and/or crystallization. $[\alpha] = [\alpha]_D^{20}$ in methanol, c = 1.

Example 1

The pH of a mixture of 978 mg of 2-[1S-(3S-hydroxy-4S-(N-tert.-butoxycarbonyl-L-phenylalanyl-N(imi)-(2,4-dinitrophenyl)-L-histidylamino)-5-cyclohexylpentanoylamino)-3-methylbutyl]-3H-quinazolin-4-one ["2-[1S-(BOC-Phe-imi-DNP-His-AHCP-amino)-3-methylbutyl]-3H-quinazolin-4-one"; obtainable by reacting BOC-Leu-OH with methyl anthranilate to give methyl 2-(BOC-Leu-amino)-benzoate (oil), reacting the latter with hydrazine hydrate to give 2-(1S-BOC-amino-3-methylbutyl)-3-amino-3H-quinazolin-4-one (m.p. 110-115° (decomp.); [α] -47.1°), boiling the latter for 5 hours with Raney Ni in isopropanol with the formation of 2-(1S-BOC-amino-3-methylbutyl)-3H-quinazolin-4-one (m.p. 215° (decomp.); [α] -48.5°), splitting off the BOC group by means of 4N HCl in dioxane to give 2-(1S-amino-3-methylbutyl)-3H-quinazolin-4-one (dihydrochloride, m.p. 275° (decomp.); [α] -28.4°), reacting the latter with BOC-AHCP-OH/DCCI/HOBt to give 2-(1S-BOC-AHCP-amino-3-methylbutyl)-3H-quinazolin-4-one, splitting off the BOC group and subjecting the product to a condensation reaction with BOC-imi-DNP-His-OH to give 2-(1S-BOC-imi-DNP-His-AHCP-amino-3-methylbutyl)-3H-quinazolin-4-one, splitting off the BOC group again and reacting the product with BOC-Phe-OH], 2 g of 2-mercaptoethanol, 20 ml of DMF and 20 ml of water is adjusted to 8 by stirring with aqueous Na_2CO_3 solution at 20°, and the

mixture is stirred for 2 hours at 20°. Working up in the customary manner gives 2-[1S-(3S-hydroxy-4S-(N-tert.-butoxycarbonyl-L-phenylalanyl-L-histidylamino)-5-cyclohexylpentanoylamino)-3-methylbutyl]-3H-quinazolin-4-one ["2-[1S-(BOC-Phe-His-AHCP-amino)-3-methylbutyl]-3H-quinazolin-4-one"], m.p. 147-149°.

The following are obtained analogously by cleaving the corresponding imi-DNP derivatives:

3-(BOC-Phe-His-AHCP-Ile-amino)-propane-1,2-diol, m.p. 180-182°

3-(BOC-Phe-His-AHCP-Leu-amino)-propane-1,2-diol

2-(BOC-Phe-His-AHCP-Ile-amino)-ethanesulfonamide, m.p. 182°

2-(BOC-Phe-His-AHCP-Leu-amino)-ethanesulfonamide

o-(BOC-Phe-His-AHCP-Ile-amino)-benzenesulfonamide

o-(BOC-Phe-His-AHCP-Leu-amino)-benzenesulfonamide

m-(BOC-Phe-His-AHCP-Ile-amino)-benzenesulfonamide

m-(BOC-Phe-His-AHCP-Leu-amino)-benzenesulfonamide

N^4-(BOC-Phe-His-AHCP-Ile)-sulfanilamide

N^4-(BOC-Phe-His-AHCP-Leu)-sulfanilamide, m.p. 146-147°

p-(BOC-Phe-His-AHCP-Ile-aminomethyl)-benzenesulfonamide, m.p. 227°

p-[2-(BOC-Phe-His-AHCP-Ile-amino)-ethyl]-benzenesulfonamide,

o-(BOC-Phe-His-AHCP-Ile-amino)-benzenesulfoni acid N-methylamide

o-(BOC-Phe-His-AHCP-Leu-amino)-benzenesulfonic acid N-methylamide

m-(BOC-Phe-His-AHCP-Ile-amino)-benzenesulfonic acid N-methylamide

m-(BOC-Phe-His-AHCP-Leu-amino)-benzenesulfonic acid N-methylamide

p-(BOC-Phe-His-AHCP-Ile-amino)-benzenesulfonic acid N-methylamide, m.p. 157°

p-(BOC-Phe-His-AHCP-Leu-amino)-benzenesulfonic acid N-methylamide

o-(BOC-Phe-His-AHCP-Ile-amino)-benzenesulfonic acid N,N-dimethylamide

o-(BOC-Phe-His-AHCP-Leu-amino)-benzenesulfonic acid N,N-

dimethylamide

m-(BOC-Phe-His-AHCP-Ile-amino)-benzenesulfonic acid N,N-dimethylamide

m-(BOC-Phe-His-AHCP-Leu-amino)-benzenesulfonic acid N,N-dimethylamide

p-(BOC-Phe-His-AHCP-Ile-amino)-benzenesulfonic acid N,N-dimethylamide, m.p. 168°

p-(BOC-Phe-His-AHCP-Leu-amino)-benzenesulfonic acid N,N-dimethylamide

o-(morpholinoacetyl-Phe-His-AHCP-Ile-amino)-benzenesulfonamide

o-(morpholinoacetyl-Phe-His-AHCP-Leu-amino)-benzenesulfonamide

m-(morpholinoacetyl-Phe-His-AHCP-Ile-amino)-benzenesulfonamide

m-(morpholinoacetyl-Phe-His-AHCP-Leu-amino)-benzenesulfonamide

p-(morpholinoacetyl-Phe-His-AHCP-Ile-amino)-benzenesulfonamide

p-(morpholinoacetyl-Phe-His-AHCP-Leu-amino)-benzenesulfonamide

o-(morpholinoacetyl-Phe-His-AHCP-Ile-amino)-benzenesulfonic acid N-methylamide

o-(morpholinoacetyl-Phe-His-AHCP-Leu-amino)-benzenesulfonic acid N-methylamide

m-(morpholinoacetyl-Phe-His-AHCP-Ile-amino)-benzenesulfonic acid N-methylamide

m-(morpholinoacetyl-Phe-His-AHCP-Leu-amino)-benzenesulfonic acid N-methylamide

p-(morpholinoacetyl-Phe-His-AHCP-Ile-amino)-benzenesulfonic acid N-methylamide

p-(morpholinoacetyl-Phe-His-AHCP-Leu-amino)-benzenesulfonic acid N-methylamide

o-(morpholinoacetyl-Phe-His-AHCP-Ile-amino)-benzenesulfonic acid N,N-dimethylamide

o-(morpholinoacetyl-Phe-His-AHCP-Leu-amino)-benzenesulfonic acid N,N-dimethylamide

m-(morpholinoacetyl-Phe-His-AHCP-Ile-amino)-benzenesulfonic acid N,N-dimethylamide

m-(morpholinoacetyl-Phe-His-AHCP-Leu-amino)-benzenesulfonic acid N,N-dimethylamide

p-(morpholinoacetyl-Phe-His-AHCP-Ile-amino)-benzenesulfonic acid N,N-dimethylamide

p-(morpholinoacetyl-Phe-His-AHCP-Leu-amino)-benzenesulfonic acid N,N-dimethylamide

5-(BOC-Phe-His-AHCP-Ile-amino)-furan-2-sulfonamide

5-(BOC-Phe-His-AHCP-Leu-amino)-furan-2-sulfonamide

5-(BOC-Phe-His-AHCP-Ile-amino)-thiophene-2-sulfonamide

5-(BOC-Phe-His-AHCP-Leu-amino)-thiophene-2-sulfonamide

5-(BOC-Phe-His-AHCP-Ile-amino)-thiophene-3-sulfonamide

5-(BOC-Phe-His-AHCP-Leu-amino)-thiophene-3-sulfonamide

2-(BOC-Phe-His-AHCP-Ile-amino)-pyridine-5-sulfonamide

2-(BOC-Phe-His-AHCP-Leu-amino)-pyridine-5-sulfonamide

p-(BOC-Phe-His-AHCP-Ile-amino)-benzamide, m.p. 228°

p-(BOC-Phe-His-AHCP-Leu-amino)-benzamide

p-(BOC-Phe-His-AHCP-Ile-amino)-benzenephosphonic acid diamide

p-(BOC-Phe-His-AHCP-Leu-amino)-benzenephosphonic acid diamide

2-[1S-(BOC-Phe-His-AHCP-amino)-ethyl]-3H-quinazolin-4-one

2-[1S-(BOC-Phe-His-AHCP-amino)-ethyl]-3-amino-3H-quinazolin-4-one [obtainable via methyl 2-(BOC-Ala-amino)-benzoate (m.p. 110-112°)]

2-[1S-(BOC-Phe-His-AHCP-amino)-2-methylpropyl]-3H-quinazolin-4-one

2-[1S-(BOC-Phe-His-AHCP-amino)-2-methylpropyl]-3-amino-3H-quinazolin-4-one, m.p. 127° [obtainable via methyl 2-(BOC-Val-amino)-benzoate (m.p. 151-155°)]

2-[1S-(BOC-Phe-His-AHCP-amino)-2S-methylbutyl]-3H-quinazolin-4-one

2-[1S-(BOC-Phe-His-AHCP-amino)-2S-methylbutyl]-3-amino-3H-quinazolin-4-one, m.p. 120° [decomp.; obtainable via 2-(1S-BOC-amino-2S-methylbutyl)-3-amino-3H-quinazolin-4-one

(m.p. 110-115°; [α] -41.9°) and 2-(1S-amino-2S-methylbutyl)-3-amino-3H-quinazolin-4-one (m.p. 105° (decomp.); [α] -4.4°]

2-[1S-(BOC-Phe-His-AHCP-amino)-3-methylbutyl]-3-amino-3H-quinazolin-4-one, m.p. 125-128°

2-[1S-(BOC-Phe-His-AHCP-amino)-2-phenylethyl]-3H-quinazolin-4-one

2-[1S-(BOC-Phe-His-AHCP-amino)-2-phenylethyl]-3-amino-3H-quinazolin-4-one, m.p. 198° [obtainable via methyl 2-(BOC-Phe-amino)-benzoate (m.p. 145-147°)]

2-[1S-(BOC-Phe-His-AHCP-amino)-2S-methylbutyl]-6-sulfamoyl-7-chloro-3H-quinazolin-4-one

2-[1S-(BOC-Phe-His-AHCP-amino)-2S-methylbutyl]-3-amino-6-sulfamoyl-7-chloro-3H-quinazolin-4-one

2-[1S-(BOC-Phe-His-AHCP-amino)-3-methylbutyl]-6-sulfamoyl-7-chloro-3H-quinazolin-4-one

2-[1S-(BOC-Phe-His-AHCP-amino)-3-methylbutyl]-3-amino-6-sulfamoyl-7-chloro-3H-quinazolin-4-one

2-[1S-(N-(2-pyrrolidino-3-phenyl-propionyl)-His-AHCP-amino)-2S-methylbutyl]-3H-quinazolin-4-one

2-[1S-(N-(2-pyrrolidino-3-phenyl-propionyl)-His-AHCP-amino)-2S-methylbutyl]-3-amino-3H-quinazolin-4-one

2-[1S-(N-(2-pyrrolidino-3-phenyl-propionyl)-His-AHCP-amino)-3-methylbutyl]-3H-quinazolin-4-one

2-[1S-(N-(2-pyrrolidino-3-phenyl-propionyl)-His-AHCP-amino)-3-methylbutyl]-3-amino-3H-quinazolin-4-one

2-[1S-(N-(2-piperidino-3-phenyl-propionyl)-His-AHCP-amino)-2S-methylbutyl]-3H-quinazolin-4-one

2-[1S-(N-(2-piperidino-3-phenyl-propionyl)-His-AHCP-amino)-2S-methylbutyl]-3-amino-3H-quinazolin-4-one

2-[1S-(N-(2-piperidino-3-phenyl-propionyl)-His-AHCP-amino)-3-methylbutyl]-3H-quinazolin-4-one

2-[1S-(N-(2-piperidino-3-phenyl-propionyl)-His-AHCP-amino)-3-methylbutyl]-3-amino-3H-quinazolin-4-one

2-[1S-(N-(2-morpholino-3-phenyl-propionyl)-His-AHCP-amino)-2S-methylbutyl]-3H-quinazolin-4-one

2-[1S-(N-(2-morpholino-3-phenyl-propionyl)-His-AHCP-amino)-2S-methylbutyl]-3-amino-3H-quinazolin-4-one

2-[1S-(N-(2-morpholino-3-phenyl-propionyl)-His-AHCP-amino)-3-methylbutyl]-3H-quinazolin-4-one

2-[1S-(N-(2-morpholino-3-phenyl-propionyl)-His-AHCP-amino)-3-methylbutyl]-3-amino-3H-quinazolin-4-one

2-[1S-(N-(2-benzyl-hexanoyl)-His-AHCP-amino)-2S-methyl-butyl]-3H-quinazolin-4-one

2-[1S-(N-(2-benzyl-hexanoyl)-His-AHCP-amino)-2S-methyl-butyl]-3-amino-3H-quinazolin-4-one

2-[1S-(N-(2-benzyl-hexanoyl)-His-AHCP-amino)-3-methyl-butyl]-3H-quinazolin-4-one

2-[1S-(N-(2-benzyl-hexanoyl)-His-AHCP-amino)-3-methyl-butyl]-3-amino-3H-quinazolin-4-one

2-[1S-(N-(2-butoxy-3-phenyl-propionyl)-His-AHCP-amino)-2S-methylbutyl]-3H-quinazolin-4-one

2-[1S-(N-(2-butoxy-3-phenyl-propionyl)-His-AHCP-amino)-2S-methylbutyl]-3-amino-3H-quinazolin-4-one

2-[1S-(N-(2-butoxy-3-phenyl-propionyl)-His-AHCP-amino)-3-methylbutyl]-3H-quinazolin-4-one

2-[1S-(N-(2-butoxy-3-phenyl-propionyl)-His-AHCP-amino)-3-methylbutyl]-3-amino-3H-quinazolin-4-one

2-[1S-(N-(2-butylthio-3-phenyl-propionyl)-His-AHCP-amino)-2S-methylbutyl]-3H-quinazolin-4-one

2-[1S-(N-(2-butylthio-3-phenyl-propionyl)-His-AHCP-amino)-2S-methylbutyl]-3-amino-3H-quinazolin-4-one

2-[1S-(N-(2-butylthio-3-phenyl-propionyl)-His-AHCP-amino)-3-methylbutyl]-3H-quinazolin-4-one

2-[1S-(N-(2-butylthio-3-phenyl-propionyl)-His-AHCP-amino)-3-methylbutyl]-3-amino-3H-quinazolin-4-one

Example 2

1 g of 2-[1S-(BOC-Phe-(imi-BOM-His)-AHCP-amino)-2S-methylbutyl]-3-amino-3H-quinazoline-4-one [m.p. 146°; [α] -37.2°; obtainable from 2-(1S-amino-2S-methylbutyl)-3-amino-3H-quinazolin-4-one and BOC-Phe-(imi-BOM-His)-AHCP-OH] is dissolved in 15 ml of methanol, and the mixture is hydrogenated over 0.5 % Pd/C at 20° and 1 bar until absorption ceases, and is filtered and evaporated

(BOC-Phe-His-AHCP-amino)-2S-methylbutyl]-3-amino-3H-quinazolin-4-one, m.p. 120° (decomp.).

The other compounds indicated in Example 1 are obtained analogously by cleaving the corresponding imi-BOM derivatives, as are also the following:

p-(BOC-Phe-His-AHCP-Ile-amino)-benzenesulfonanilide
p-(BOC-Phe-His-AHCP-Ile-amino)-benzenesulfonic acid o-sulfamoylanilide
p-(BOC-Phe-His-AHCP-Ile-amino)-benzenesulfonic acid p-sulfamoylanilide
p-(BOC-Phe-His-AHCP-Ile-amino)-benzenesulfonic acid N-(2-thienyl)-amide
p-(BOC-Phe-His-AHCP-Ile-amino)-benzenesulfonic acid N-(2-thiazolyl)-amide
p-(BOC-Phe-His-AHCP-Ile-amino)-benzenesulfonic acid N-(3-isoxazolyl)-amide
p-(BOC-Phe-His-AHCP-Ile-amino)-benzenesulfonic acid N-(5-methyl-3-isoxazolyl)-amide
p-(BOC-Phe-His-AHCP-Ile-amino)-benzenesulfonic acid N-(3,4-dimethyl-5-isoxazolyl)-amide
p-(BOC-Phe-His-AHCP-Ile-amino)-benzenesulfonic acid N-(4-pyridyl)-amide
p-(BOC-Phe-His-AHCP-Ile-amino)-benzenesulfonic acid N-(2-pyrimidinyl)-amide, m.p. 192°
p-(BOC-Phe-His-AHCP-Ile-amino)-benzenesulfonic acid N-(4-methyl-2-pyrimidinyl)-amide
p-(BOC-Phe-His-AHCP-Ile-amino)-benzenesulfonic acid N-(4,6-dimethyl-2-pyrimidinyl)-amide
p-(BOC-Phe-His-AHCP-Ile-amino)-benzenesulfonic acid N-(2,6-dimethyl-4-pyrimidinyl)-amide.

Example 3

1.01 g of N-methylmorpholine is added to a solution, in 60 ml of CH_2Cl_2, of 4.58 g of 3-(H-Gly-AHCP-Ile-amino)-propane-1,2-diol [obtainable by reacting BOC-Gly-AHCP-OH with 3-(H-Ile-amino)-propane-1,2-diol to give 3-(BOC-Gly-AHCP-Ile-amino)-propane-1,2-diol and splitting off the BOC group]. 2.65 g of BOC-Phe-OH, 1.35 g of HOBt and

a solution of 2.06 g of DCCI in 50 ml of CH_2Cl_2 are added with stirring, the mixture is stirred for 14 hours at 4°, the precipitated dicyclohexylurea is filtered off and the filtrate is evaporated. Customary working up gives 3-(BOC-Phe-Gly-AHCP-Ile-amino)-propane-1,2-diol, m.p. 104-106°.

Example 4

N^4-(BOC-Phe-Gly-AHCP-Leu)-sulfanilamide, m.p. 142-144°, is obtained analogously to Example 3 from BOC-Phe-Gly-OH and N^4-(H-AHCP-Leu)-sulfanilamide.

The following are obtained analogously:

N^4-(BOC-Phe-Gly-AHCP-Ile)-sulfanilamide

N^4-(POA-Phe-Abu-AHCP-Leu)-sulfanilamide

N^4-(ETOC-Phe-Ada-AHCP-Leu)-sulfanilamide

N^4-(IPOC-Phe-Ala-AHCP-Leu)-sulfanilamide

N^4-(CBZ-Phe-Cal-AHCP-Leu)-sulfanilamide

N^4-(acetyl-Phe-(N-im-methyl-His)-AHCP-Leu)-sulfanilamide

N^4-(ETNC-Phe-Ile-AHCP-Leu)-sulfanilamide

N^4-(IPNC-Phe-Leu-AHCP-Leu)-sulfanilamide

N^4-(MC-Phe-tert.-Leu-AHCP-Leu)-sulfanilamide

N^4-(PBB-Phe-Met-AHCP-Leu)-sulfanilamide

N^4-(4-phenylbutyryl-Phe-αNal-AHCP-Leu)-sulfanilamide

N^4-(2-benzyl-3-phenylpropionyl-Phe-βNal-AHCP-Leu)-sulfanilamide

N^4-(morpholinoacetyl-Phe-βAla-AHCP-Leu)-sulfanilamide, m.p. 192°

N^4-[2-(2-phenylethyl)-4-phenylbutyryl-Phe-Nbg-AHCP-Leu]-sulfanilamide

N^4-[2-(2-naphthylmethyl)-4-phenylbutyryl-Phe-Nle-AHCP-Leu]-sulfanilamide

N^4-[propionyl-Phe-(N-Me-His)-AHCP-Leu]-sulfanilamide

N^4-[butyryl-Phe-(N-Me-Phe)-AHCP-Leu]-sulfanilamide

N^4-(isobutyryl-Phe-Phe-AHCP-Leu)-sulfanilamide

N^4-(cyclopentylcarbonyl-Phe-Pro-AHCP-Leu)-sulfanilamide

N^4-(cyclohexylcarbonyl-Phe-Ser-AHCP-Leu)-sulfanilamide

N^4-(benzoyl-Phe-Thr-AHCP-Leu)-sulfanilamide

N^4-(phenylacetyl-Phe-Tic-AHCP-Leu)-sulfanilamide

N^4-(2-phenylpropionyl-Phe-Trp-AHCP-Leu)-sulfanilamide

N^4-(3-phenylpropionyl-Phe-Tyr-AHCP-Leu)-sulfanilamide

N^4-(2-p-fluorophenylpropionyl-Phe-Val-AHCP-Leu)-sulfanil-

Example 5

N^4-(BOC-Phe-Gly-AHCP-Leu)-sulfanilamide, m.p. 142-144°, is obtained analogously to Example 3 from BOC-Phe-Gly-AHCP-OH and N^4-(H-Leu)-sulfanilamide.

The following are obtained analogously:

N^4-(BOC-Phe-BAla-AHCP-Leu)-sulfanilamide, m.p. 196°

N^4-(BOC-Phe-Gly-AHCP-Ile)-sulfanilamide

5-(BOC-Phe-Gly-AHCP-Ile-amino)-thiophene-3-sulfonamide

2-[1S-(BOC-Phe-Gly-AHCP-amino)-2-methylpropyl]-3H-quinazolin-4-one

2-[1S-(BOC-Phe-Gly-AHCP-amino)-2-methylpropyl]-3-amino-3H-quinazolin-4-one

2-[1S-(BOC-Phe-Gly-AHCP-amino)-2S-methylbutyl]-3H-quinazolin-4-one

2-[1S-(BOC-Phe-Gly-AHCP-amino)-2S-methylbutyl]-3-amino-3H-quinazolin-4-one, m.p. 115° (decomp.)

2-[1S-(BOC-Phe-Gly-AHCP-amino)-3-methylbutyl]-3H-quinazolin-4-one

2-[1S-(BOC-Phe-Gly-AHCP-amino)-3-methylbutyl]-3-amino-3H-quinazolin-4-one

2-[1S-(BOC-Phe-Gly-AHCP-amino)-2-phenylethyl]-3H-quinazolin-4-one

2-[1S-(BOC-Phe-Gly-AHCP-amino)-2-phenylethyl]-3-amino-3H-quinazolin-4-one

2-[1S-(BOC-Phe-Gly-AHCP-amino)-2S-methylbutyl]-6-sulfamoyl-7-chloro-3H-quinazolin-4-one

2-[1S-(BOC-Phe-Gly-AHCP-amino)-2S-methylbutyl]-3-amino-6-sulfamoyl-7-chloro-3H-quinazolin-4-one

2-[1S-(BOC-Phe-Gly-AHCP-amino)-3-methylbutyl]-6-sulfamoyl-7-chloro-3H-quinazolin-4-one

2-[1S-(BOC-Phe-Gly-AHCP-amino)-3-methylbutyl]-3-amino-6-sulfamoyl-7-chloro-3H-quinazolin-4-one

2-(BOC-Phe-Gly-AHCP-Ile-aminomethyl)-3H-quinazolin-4-one

2-(BOC-Phe-Gly-AHCP-Ile-aminomethyl)-3-amino-3H-quinazolin-4-one, m.p. 188°

2-[1S-(N-(2-pyrrolidino-3-phenyl-propionyl)-Gly-AHCP-amino)-2S-methylbutyl]-3H-quinazolin-4-one

2-[1S-(N-(2-pyrrolidino-3-phenyl-propionyl)-Gly-AHCP-amino)-

2-[1S-(N-(2-pyrrolidino-3-phenyl-propionyl)-Gly-AHCP-amino)-3-methylbutyl]-3H-quinazolin-4-one

2-[1S-(N-(2-pyrrolidino-3-phenyl-propionyl)-Gly-AHCP-amino)-3-methylbutyl]-3-amino-3H-quinazolin-4-one

2-[1S-(N-(2-piperidino-3-phenyl-propionyl)-Gly-AHCP-amino)-2S-methylbutyl]-3H-quinazolin-4-one

2-[1S-(N-(2-piperidino-3-phenyl-propionyl)-Gly-AHCP-amino)-2S-methylbutyl]-3-amino-3H-quinazolin-4-one

2-[1S-(N-(2-piperidino-3-phenyl-propionyl)-Gly-AHCP-amino)-3-methylbutyl]-3H-quinazolin-4-one

2-[1S-(N-(2-piperidino-3-phenyl-propionyl)-Gly-AHCP-amino)-3-methylbutyl]-3-amino-3H-quinazolin-4-one

2-[1S-(N-(2-morpholino-3-phenyl-propionyl)-Gly-AHCP-amino)-2S-methylbutyl]-3H-quinazolin-4-one

2-[1S-(N-(2-morpholino-3-phenyl-propionyl)-Gly-AHCP-amino)-2S-methylbutyl]-3-amino-3H-quinazolin-4-one

2-[1S-(N-(2-morpholino-3-phenyl-propionyl)-Gly-AHCP-amino)-3-methylbutyl]-3H-quinazolin-4-one

2-[1S-(N-(2-morpholino-3-phenyl-propionyl)-Gly-AHCP-amino)-3-methylbutyl]-3-amino-3H-quinazolin-4-one

2-[1S-(N-(2-benzyl-hexanoyl)-Gly-AHCP-amino)-2S-methyl-butyl]-3H-quinazolin-4-one

2-[1S-(N-(2-benzyl-hexanoyl)-Gly-AHCP-amino)-2S-methyl-butyl]-3-amino-3H-quinazolin-4-one

2-[1S-(N-(2-benzyl-hexanoyl)-Gly-AHCP-amino)-3-methyl-butyl]-3H-quinazolin-4-one

2-[1S-(N-(2-benzyl-hexanoyl)-Gly-AHCP-amino)-3-methyl-butyl]-3-amino-3H-quinazolin-4-one

2-[1S-(N-(2-butoxy-3-phenyl-propionyl)-Gly-AHCP-amino)-2S-methylbutyl]-3H-quinazolin-4-one

2-[1S-(N-(2-butoxy-3-phenyl-propionyl)-Gly-AHCP-amino)-2S-methylbutyl]-3-amino-3H-quinazolin-4-one

2-[1S-(N-(2-butoxy-3-phenyl-propionyl)-Gly-AHCP-amino)-3-methylbutyl]-3H-quinazolin-4-one

2-[1S-(N-(2-butoxy-3-phenyl-propionyl)-Gly-AHCP-amino)-3-methylbutyl]-3-amino-3H-quinazolin-4-one

2-[1S-(N-(2-butylthio-3-phenyl-propionyl)-Gly-AHCP-amino)-

2S-methylbutyl]-3H-quinazolin-4-one
2-[1S-(N-(2-butylthio-3-phenyl-propionyl)-Gly-AHCP-amino)-2S-methylbutyl]-3-amino-3H-quinazolin-4-one
2-[1S-(N-(2-butylthio-3-phenyl-propionyl)-Gly-AHCP-amino)-3-methylbutyl]-3H-quinazolin-4-one
2-[1S-(N-(2-butylthio-3-phenyl-propionyl)-Gly-AHCP-amino)-3-methylbutyl]-3-amino-3H-quinazolin-4-one

Example 6

3-(BOC-Phe-Gly-AHCP-Ile-Met-amino)-propane-1,2-diol is obtained analogously to Example 3 from BOC-Phe-Gly-AHCP-Ile-OH and 3-(H-Met-amino)-propane-1,2-diol.

Example 7

3-(BOC-Phe-Gly-AHCP-Ile-amino)-propane-1,2-diol, m.p. 104-106°, is obtained analogously to Example 3 from BOC-Phe-Gly-AHCP-Ile-OH and 3-aminopropane-1,2-diol.

The following are obtained analogously:

3-(BOC-Phe-Gly-AHCP-Abu-amino)-propane-1,2-diol
3-(BOC-Phe-Gly-AHCP-Ala-amino)-propane-1,2-diol
3-(BOC-Phe-Gly-AHCP-Cal-amino)-propane-1,2-diol
3-(BOC-Phe-Gly-AHCP-His-amino)-propane-1,2-diol
3-(BOC-Phe-Gly-AHCP-Leu-amino)-propane-1,2-diol
3-(BOC-Phe-Gly-AHCP-Met-amino)-propane-1,2-diol
3-(BOC-Phe-Gly-AHCP-Nle-amino)-propane-1,2-diol
3-(BOC-Phe-Gly-AHCP-Phe-amino)-propane-1,2-diol
3-(BOC-Phe-Gly-AHCP-Trp-amino)-propane-1,2-diol
3-(BOC-Phe-Gly-AHCP-Tyr-amino)-propane-1,2-diol
3-(BOC-Phe-Gly-AHCP-Val-amino)-propane-1,2-diol
3-(BOC-Phe-Gly-AHCH-Ile-amino)-propane-1,2-diol
3-(BOC-Phe-Gly-Sta-Ile-amino)-propane-1,2-diol
3-(BOC-Phe-Gly-AHPP-Ile-amino)-propane-1,2-diol.

Example 8

A solution of 1 g of 2-[1S-(BOC-Phe-His-AHCP-amino)-3-methylbutyl]-3H-quinazolin-4-one in 20 ml of 4N HCl in dioxane is stirred for 30 minutes at 20° and is then evaporated. This gives 2-[1S-(H-Phe-His-AHCP-amino)-3-methylbutyl]-3H-quinazolin-4-one.

The following are obtained analogously by cleaving the corresponding BOC derivatives:

3-(H-Phe-Gly-AHCP-Ile-amino)-propane-1,2-diol
3-(H-Phe-His-AHCP-Ile-amino)-propane-1,2-diol
N^4-(H-Phe-Gly-AHCP-Leu)-sulfanilamide
N^4-(H-Phe-His-AHCP-Leu)-sulfanilamide

2-[1S-(H-Phe-His-AHCP-amino)-3-methylbutyl]-3-amino-3H-quinazolin-4-one
2-[1S-(H-Phe-His-AHCP-amino)-2S-methylbutyl]-3H-quinazolin-4-one
2-[1S-(H-Phe-His-AHCP-amino)-2S-methylbutyl]-3-amino-3H-quinazolin-4-one.

Example 9

1 g of 2-[1S-(CBZ-Phe-His-AHCP-amino)-3-methylbutyl]-3H-quinazolin-4-one is dissolved in 15 ml of ethanol, and the mixture is hydrogenated over 0.5 g of 10% Pd/C at 20° and 1 bar for 3 hours and is filtered and evaporated to give, after purification by chromatography, 2-[1S-(H-Phe-His-AHCP-amino)-3-methylbutyl]-3H-quinazolin-4-one.

Example 10

70 mg of hydroxylamine hydrochloride are added to a solution of 826 mg of 2-[1S-(3-Oxo-4S-BOC-Phe-His-amino-5-cyclohexylpentanoylamino)-3-methylbutyl]-3H-quinazolin-4-one and 1.43 g of Na_2CO_3 . 10 H_2O in 5 ml of methanol and 5 ml of water, and the mixture is stirred for 14 hours at 20°. The precipitated oxime is filtered off, dried, dissolved in 10 ml of methanol and hydrogenated over 0.5 g of Raney Ni at 20° and 5 bar. The catalyst is filtered off, the filtrate is evaporated and the resulting mixture is separated over silica gel to give 2-[1S-(3S-amino-4S-BOC-Phe-His-amino-5-cyclohexylpentanoylamino)-3-methylbutyl]-3H-quinazolin-4-one ["2-[1S-(BOC-Phe-His-DACP-amino)-3-methylbutyl]-3H-quinazolin-4-one"]; the 3R-amino epimer is also obtained.

The following are obtained analogously from the corresponding oxo compounds:

2-[1S-(BOC-Phe-His-DACH-amino)-3-methylbutyl]-3H-quinazolin-4-one

2-[1S-(BOC-Phe-His-DAMH-amino)-3-methylbutyl]-3H-quinazolin-4-one

2-[1S-(BOC-Phe-His-DAPP-amino)-3-methylbutyl]-3H-quinazolin-4-one.

Example 11

0.5 g of Raney nickel, moistened with 0.5 g of isopropanol, is added to a solution of 1 g of 2-[1S-(BOC-Phe-His-AHCP-amino)-3-methylbutyl]-3-amino-3H-quinazolin-4-one in 500 ml of isopropanol, and the mixture is boiled for 5 hours. After filtration, the mixture is evaporated and worked up in the customary manner to give 2-[1S-(BOC-Phe-His-AHCP-amino)-3-methylbutyl]-3H-quinazolin-4-one, m.p. 147-149°.

The examples below relate to pharmaceutical formulations.

Example A: Injection vials

The pH of a solution of 100 g of 2-[1S-(BOC-Phe-His-AHCP-amino)-3-methylbutyl]-3H-quinazolin-4-one and 5 g of disodium hydrogenphosphate in 4 l of twice distilled water is adjusted to 6.5 with 2N hydrochloric acid, and the solution is filtered under sterile conditions and filled into injection vials. These are lyophilized under sterile conditions and closed in a sterile manner. Each injection vial contains 500 mg of active compound.

Example B: Suppositories

A mixture of 50 g of 2-[1S-(BOC-Phe-His-AHCP-amino)-3-methylbutyl]-3-amino-3H-quinazolin-4-one with 10 g of soya lecithin and 140 g of cocoa butter is melted, poured into moulds and allowed to cool. Each suppository contains 250 mg of active compound.

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The claims defining the invention are as follows:

1. Amino acid derivatives of the formula I

$$X\text{-}Z\text{-}NR^2\text{-}CHR^3\text{-}CR^4\text{-}(CHR^5)_n\text{-}CO\text{-}E\text{-}NR^6\text{-}D \qquad I$$

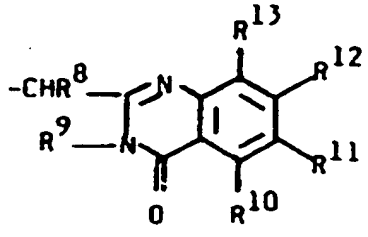
wherein

X is H, $R^1\text{-}O\text{-}C_mH_{2m}\text{-}CO\text{-}$, $R^1\text{-}C_mH_{2m}\text{-}O\text{-}CO\text{-}$, $R^1\text{-}C_mH_{2m}\text{-}CO\text{-}$, $R^1\text{-}SO_2\text{-}$ or $(R^1\text{-}C_mH_{2m}\text{-}(T)_x\text{-}C_rH_{2r})\text{-}L(R^7\text{-}C_pH_{2p})\text{-}C_tH_{2t}\text{-}CO\text{-}$,

Z is 0 to 4 amino acid radicals attached to one another by a peptide linkage and selected from the group consisting of Abu, Ada, Ala, βAla, Arg, Asn, Asp, Bia, Cal, Dab, Gln, Glu, Gly, His, N(im)-alkyl-His, Ile, Leu, tert.-Leu, Lys, Met, αNal, βNal, Nbg, Nle, Orn, Phe, Pro, Ser, Thr, Tic, Trp, Tyr and Val,

E is 0 to 2 amino acid radicals attached to one another by a peptide linkage and selected from the group consisting of Abu, Ala, Cal, His, Ile, Leu, Met, Nle, Phe, Trp, Tyr and Val,

D is $-CH_2\text{-}CHOH\text{-}CH_2OH$, $-C_zH_{2z}\text{-}SO_2\text{-}R^{14}$, a phenyl-$C_yH_{2y}$-, furyl-$C_yH_{2y}$-, thienyl-$C_yH_{2y}$- or pyridyl-$C_yH_{2y}$- radical which is substituted by one or two $R^{14}\text{-}SO_2$- groups or an $R^{14}\text{-}CO$- group or an $(R^{14})_2\text{-}PO$- group and, if desired additionally by an Hal atom, or D is



R^1, R^3, R^7 and R^8 are each H, A, Ar, Ar-alkyl, Het,

Het-alkyl or cycloalkyl having 3-7 C atoms, cycloalkylalkyl having 4-11 C atoms, bicycloalkyl or tricycloalkyl having in each case 7-14 C atoms or bicycloalkylalkyl or tricycloalkylalkyl having in each case 8-18 C atoms, each of which is unsubstituted or monosubstituted or polysubstituted by A, AO and/or Hal,

R^2, R^5 and R^6 are each H or A,

R^4 is (H, OH), (H, NH_2) or =O,

R^9 is H, NH_2, NHA or NA_2,

R^{10}, R^{11}, R^{12} and R^{13} are each H, Hal, OH, OA, NH_2, SH, SA, SO_2NH_2, CF_3, CN, COOH or COOA,

R^{14} is OH, OA, NH_2, NHA, NA_2, NHcycloalkyl having 3-7 C atoms, N(cycloalkyl)$_2$ having 6-14 C atoms, pyrrolidino, piperidino, hexahydroazepino, morpholino, thiomorpholino, piperazino, N-A-piperazino, NHAr or NHHet,

L is CH or N,

T is O, S, NH or NA,

n is 1 or 2,

m, p, r and t are each 0, 1, 2, 3, 4 or 5,

x is 0 or 1,

y is 0, 1 or 2,

z is 2, 3, 4, 5 or 6,

Ar is phenyl which is unsubstituted or monosubstituted or polysubstituted by A, AO, Hal, CF_3, OH, H_2NSO_2 and/or NH_2 or unsubstituted naphthyl,

Het is a saturated or unsaturated 5-membered or 6-membered heterocyclic radical which has 1-4 N, O and/or S atoms, which can be condensed with a benzene ring and/or can be monosubstituted or polysubstituted by A, AO, Hal, CF_3, HO, O_2N, carbonyl oxygen, H_2N, HAN, A_2N, AcNH, AS, ASO, ASO_2, HOOC, AOOC, CN, H_2NCO, H_2NSO_2, ASO_2NH, Ar or Ar-alkenyl, hydroxyalkyl and/or aminoalkyl having in each case 1-8 C atoms, and/or in which the N and/or S heteroatoms can also be oxidized,

Hal is F, Cl, Br or I,

Ac is A-CO-, Ar-CO- or A-NH-CO-,
alkyl- is an alkylene group having 1-4 C atoms and
A is alkyl having 1-8 C atoms,
and wherein it is also possible for one or more -NA-CO- groups to replace one or more -NH-CO- groups, and salts thereof.

2. a) 2-[1S-(BOC-Phe-His-AHCP-amino)-2S-methyl-butyl]-3H-quinazol in-4-one;
b) 2-[1S-(BOC-Phe-His-AHCP-amino)-2S-methyl-butyl]-3-amino-3H-quinazol in-4-one;
c) 2-[1S-(BOC-Phe-His-AHCP-amino)-3-methyl-butyl]-3H-quinazol in-4-one; or
d) 2-[1S-(BOC-Phe-His-AHCP-amino)-3-methyl-butyl]-3-amino-3H-quinazol in-4-one.

3. Process for the preparation of an amino acid derivative of the formula I and salts thereof, characterized in that this amino acid derivative is liberated from one of its functional derivatives by treatment with a solvolysing or hydrogenolysing agent, or in that a carboxylic acid of the formula II

$X\text{-}G^1\text{-}OH$ II

wherein G^1 is (a) Z^1,
(b) Z,
(c) Z-W,
(d) $Z\text{-}W\text{-}E^1$,
(e) Z-W-E and

W is

$$-NR^2\text{-}CHR^3\text{-}CR^4\text{-}(CHR^5)_n\text{-}CO-$$

is reacted with an amino compound of the formula III

$H\text{-}G^2$ III

wherein G^2 is (a) $-Z^2\text{-}W\text{-}E\text{-}NR^6\text{-}D$,

(b) $-W-E-NR^6-D$,

(c) $-E-NR^6-D$,

(d) $-E^2-NR^6-D$,

(e) $-NR^6-D$,

E^1 and E^2 are each one amino acid radical selected from the group conisting of Abu, Ala, Cal, His, Ile, Leu, Met, Nle, Phe, Trp, Tyr and Val in such a manner that E^1 + E^2 together are E,

Z^1 and Z^2 are each 1 to 3 amino acid radicals selected from the group consisting of Abu, Ada, Ala, βAla, Arg, Asn, Asp, Bia, Cal, Dab, Gln, Glu, Gly, His N(im)-alkyl-His, Ile, Leu, tert -Leu, Lys, Met, αNal, βNal, Nbg, Nle, Orn, Phe, Pro, Ser, Thr, Tic, Trp, Tyr and Val in such a manner that Z^1 + Z^2 together are Z, and in that, if appropriate, a functionally modified amino and/or hydroxyl group in a compound of the formula I is Liberated by treatment with solvolysing or hydrogenolysing agents and/or, in order to prepare a compound of the formula I wherein R^4 = (H, OH) or (H, NH_2), an aminoketo acid derivative of the formula I wherein R^4 = 0 is reduced or reductively aminated and/or a radical D is converted into an- other radical D by treatment with esterifying, solvolysing or reducing agents and/or a compound of the formula I is converted into one of its salts by treatment with an acid.

4. Process for the preparation of pharmaceutical formulations, characterized in that a compound of the formula I and/or one of its physiologically acceptable salts is brought into a suitable dosage form together with at least one solid, liquid or semi-liquid excipient or auxiliary and, if appropriate, in combination with one or more further active compound(s).

5. Pharmaceutical formulation characterized in that it contains at least one compound of the formula I and/or one of its physiologically acceptable salts.

6. The use of compounds of the formula I or of physiologically acceptable salts thereof for the preparation of a medicament.

7. The use of compounds of the formula I or of physiologically acceptable salts thereof in combating renin-dependent hypertension or hyperaldosteronism.

DATED this 1st day of July, 1991.

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By Its Patent Attorneys
ARTHUR S. CAVE & CO.

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